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PATENT & TRADEMARK OFFICE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re: Application of: William J. Rea, et al — Attorney Docket: 16715CIP

Serial No.: 08/902,692 — Art Group Unit: 1644

Filed: July 30, 1997 — Examiner: Schwadron, R., Ph.D.

For: **AUTOGENOUS LYMPHOCYTIC FACTOR FOR MODIFICATION OF T AND B LYMPHOCYTE PARAMETERS**

DECLARATION OF DENNIS G. HOOPER, M.D., PH.D.

1. My name is Dennis G. Hooper. My office address is 8325 Walnut Hill Lane, Suite 125, Dallas, Texas, 75231. I am over 21 years of age, of sound mind, and competent to make this Declaration.

2. All of the statements made in this Declaration made on personal knowledge are true or, if made on information and belief, are believed to be true.

3. I have been asked to give an expert opinion concerning issues surrounding the patent application Serial No. 08/902,692; Filed July 30, 1997; for **Autogenous Lymphocytic Factor for Modification of T and B Lymphocyte Parameters** and specifically concerning the issues of definition of the words "donor" and "transfer factor" as used in Warren, a reference cited against the patent application.

4. I am medical physician with board certification in Anatomic and Clinical Pathology. I am a graduate of the University of Nevada School of Medicine. I interned with the U.S. Navy in Flexible Medicine and did my Pathology residency at the U.S. Naval Hospital, San Diego, California. I also hold a Ph.D. in Microbiology from the University of California, Davis.

5. My professional experience includes Chairman of Pathology at the U.S. Naval Hospital, San Diego, Advisor to the Surgeon General of the Navy for Pathology, and Medical Director to Alpha Therapeutic Corporation ("ATC"). ATC made blood products from donors and donor pools which were evaluated and approved by the FDA prior to administration to patients as therapeutic treatments. I have also held other medical directorships in Blood Banks and Transfusion Centers. I am enclosing a copy of my Curriculum Vitae with this Declaration.

6. I have evaluated the following prior to giving my opinion in these matters:

a. Original application for patent, as filed;

b. Brief for Appellants and attached Appendices;

c. Office Action dated July 15, 2005 rejecting the pending claims; and

d. References cited in the Office Action dated July 15, 2005 against the pending claims:

(i) Youdim et al. ("Treatment of Environmentally Senstivie Patients with Transfer Factor, Part I: Immunologic Studies," Youdim, et al. Clinical Ecology, Volume 7, Number 3);

(ii) Warren (US Patent No. 4,435,384);

(iii) Goust et al. (US Patent No. 4,001,080); and

(iv) Lane et al. (as copy attached to Office Action dated July 15, 2005);

e. "Amendment" to the application dated April 7, 1999;

f. "Preliminary Amendment" to the application dated December 20, 1999;

g. "Preliminary Amendment" to the application dated September 11, 2000.

7. I was requested to provide my independent expert opinion regarding issues raised by the examiner on the difference and similarities between the method of autologous donation as it is described in the patent application and the words "donor" and "transfer factor" as used in Warren.

8. The following are definitions which are pertinent to the issues.

9. Donor. The Waren patent uses the word "donor." A donor is defined by the Code of Federal Regulations 21 (CFR 21) as an individual who volunteers to donate whole blood or blood components. The donor must be healthy and carry no detectible diseases such as HIV, Hepatitis, any other viral disease or bacterial diseases. The donor must answer specific questions concerning previous exposures, travels, and illnesses. These questions help discern if the product can be further used as replacement for blood or blood products.

10. The American Association of Blood Banks ("AABB") and the FDA through the CFR 21 publication define the types of donation allowed. [1, 2] The American Medical Association's Council on Scientific Affairs also describes these donations types as well.

a. Allogeneic donation is one in which the blood or blood product is collected from a donor other than the patient who is ill, and is transfused into a patient.

b. Autologous donation is one in which the blood or blood product is removed from a patient that is ill and after manipulation, is re-introduced into that same patient.

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[1] Code of federal regulations. Title 21 CFR. Washington, DC: US Government Printing Office 1997 (revised annually).

[2] American Association of Blood Banks ("AABB"), Technical Manual, 12th Edition. Bethesda, Maryland.

11. Transfer Factor. The Warren patent also refers to the term "transfer factor". Transfer factor is one of many biologically active components from human leukocyte extracts.[3] Extracts from these types of cells contain immunologic substances that induce an immunologic response. Thus, cells or leukocytes from one patient or group of patients contain biologically active components that can induce an immune response.

12. The issues surrounding the definitions of autologous donations, allogeneic donations, and transfer factor are closely tied to the definition of tolerance, or self recognition. In autologous donations, an individual is donating lymphocytes or blood products back to themselves. In allogeneic donations, an individual is donating lymphocytes or blood products into another recipient.

13. Transfer factor is an immune substance which is collected and transferred from donor(s) to recipients. There is no autologous donation associated with transfer factor. In its simplest form, peripheral tolerance might arise as a result of 'ignorance', as potential auto-antigens that remain hidden or sequestered from the immune system cannot induce auto-reactivity. This has been demonstrated by a variety of investigators.[4, 5, 6] As auto-antigens develop, the surrounding lymphocytes have receptors to self antigens that are sequestered; thus, lymphocytes do not recognize those antigens and no immunologic response occurs. If other allogeneic antigens come in contact with another individual lymphocytes, an immune response can occur.

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[3] Youdim et al. ("Treatment of Environmentally Senstivie Patients with Transfer Factor, Part I: Immunologic Studies," Youdim, et al. Clinical Ecology, Volume 7, Number 3), and the references cited therein.

[4] Kappler, J.W., Roehm, N. and Marrack, P. (1987) T cell tolerance by clonal elimination in the thymus. Cell 49, 273-280.

[5] Mondino, A., Khoruts, A. and Jenkins, M.K. (1996) The anatomy of T-cell activation and tolerance. Proc Natl Acad Sci USA 93, 2245-2252.

[6] Jones, L.A. et al. (1990) Peripheral clonal elimination of functional T cells. Science 250, 1726-1729, PubMed.

14. Autologous refers to self. If "self" cells are re-injected into self (same individual), then no immune response would occur because of the "ignorance" or "tolerance" of the sequestered immune receptors. Thus, the removal of lymphocytes from an individual and re-injecting them back into the patient (as is explained in this patent process) is different that injecting allogeneic antigens from a different individual.

15. Transfer factor is the substance obtained from allogeneic human leukocyte extracts and injected into another allogeneic recipient; thus, the concept of "immune ignorance" or "tolerance" is not maintained.

16. The Warren patent states that: "Transfer factor is obtained from the lymphocytes of a donor having no history of recurrent infection by herpes virus." (Col. 2, lines 35-37) and that the process in Warren includes the step: "1. Obtain a heparinized whole blood sample from a suitable donor." (Col. 2, lines 47-50).

17. The Warren patent teaches that transfer factor is obtained from any individual who has no history of a recurrent infection, specifically herpes virus. All cases sited in the Warren patent are patients with herpes simplex or condylomatous growth, not otherwise specified. Transfer factor was prepared by removing lymphocytes from a "suitable donor" that does not have a history of recurrent infection by herpes virus. Transfer factor was obtained from these lymphocytes that have been removed from any other patient other than that one with the viral infection, i.e., an allogeneic donor, not an autologous donor. Thus, transfer factor as taught by Warren did not have any relationship or association with autologous donation.

18. It is clear that Warren's patent taught that transfer factor was to be used topically on patients with viral infections. Warren excluded taking cells from any patient with a history of such a viral infection. Thus, a routineer can not draw the conclusion that any source of lymphocytes can be used. The lymphocytes simply must come from any patient other than the patient being treated for such a skin infection.

19. Based on the accepted definition of "transfer factor" as being allogeneic and based on the concern for allogeneic donor issues in Warren (i.e., no history of herpes virus and concern for using "a suitable" donor), in my opinion the proper understanding of the terms "donor" and "transfer factor" in Warren is solely in the context of allogeneic donation. Warren does not disclose or suggest autologous donation.

20. Similarly, Youdim et al, teaches that transfer factor is obtained from peripheral blood from random normal healthy donors. Isolated leukocytes from these donors were pooled, lysed and an extract prepared. Thus, transfer factor from these patients is not autologous cell isolates.

21. Goust et al, teaches that transfer factor may be obtained from lymphoblastoid cells obtained by modification of lymphocytes derived either from man or from animals other than man may be employed; thus, the product obtained is from an allogeneic donor, not an autologous donor.

22. It is apparent to this reviewer that Youdim et al, Warren, Goust et al., and Lane et al., do not encompass the same teachings as Rea, et al. as set forth in Claims 49-64 of the Rea et al. patent application.

23. I hereby declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and further that these statements are made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which the verified statement is directed.

Dennis G. Hooper, M.D., Ph.D.

January 16, 2006
Date

CURRICULUM VITAE

DENNIS GLENN HOOPER, M.D., Ph.D.

Citizenship: United States

Business Address: 2613 Sir Percival Lane
Lewisville, Texas 75056

EDUCATION

High School:	White Pine High School, Ely Nevada, 1967
Undergraduate:	University of Utah, Salt Lake City, Utah; B.S. Microbiology, 1973
Post Graduate:	University of Missouri, Columbia, Missouri; M.S. Microbiology, 1973
	University of California, Davis, Davis, California; Ph.D. Microbiology, 1982
Medical School:	University of Nevada, School of Medicine, Reno, Nevada; M.D., 1983
Internship:	Naval Hospital, San Diego, California; Flexible Medicine, 1983
Residency:	Naval Hospital, San Diego; California; Anatomic and Clinical Pathology, 1984-1988
	Diplomate, American Board of Pathology; Anatomic and Clinical Pathology Board, 1990; Recertified: American Board of Pathology; AP/CP 2002

LICENSE

Medical License, California, 1984 to Present
Medical License, Nevada, 1992 to Present
Medical License, Texas, 2001 to Present

SPECIALTY BOARD CERTIFICATION

Anatomic and Clinical Pathology, 1990
Recertified, AP/CP, 2001

CHRONOLOGICAL PROFESSIONAL CAREER EXPERIENCE

Present	Consultant to Environmental Health Center, Dallas, TX - Consultant in Exposures to Chemicals, Infectious Agents, and Toxins.
Present	Consultant to Various Laboratories on Quality Assurance/Risk Management/QC
2003 -2005	Head of Microbiology/Transfusion Service, Baptist Med. Center, San Antonio, TX
2002- 2003	Pathologist and Associate Professor, U of Texas, Tyler, Dept. of Pathology
2001-2002	Medical Director, DRL and ETMC Labs, Tyler, Texas
2000-Present	Expert Witness, Evaluation of Cause of Death, and aspects of Infectious Diseases
2000-2001	Martin Luther King Hospital, Los Angeles, CA, Pathologist
1996-Present	Consultant, Clinical Laboratory, US Naval Research Laboratory, Pt. Loma, San Diego, CA
1998-1999	Medical Director; Alpha Therapeutic Corporation, Los Angeles, CA
1996 - 1998	President and Medical Director; Nevada Bioscience Laboratories, Reno, NV; GLP and GMP Compliance Laboratory.
1989 –1995	Chairman, Department of Pathology, Naval Hospital, San Diego, CA
1993 - 1995	Specialty Advisor (Pathology) to Navy Surgeon General, U.S. Navy, San Diego, CA
1993 - 1995	Director; Ancillary Services; Naval Medical Center, San Diego, CA
1988 – 1994	Pathologist In-Charge, Microbiology, Blood Bank, and Immunology
1976 - 1979	Supervisor; Clinical Microbiology and Clinical Immunology Laboratories, Naval Hospital, San Diego, CA

ACADEMIC CAREER EXPERIENCE

Title	School	Dates
Assoc. Professor,	Pathology, University of Texas, Tyler, Texas	2002- 2004
Assoc. Clinical Professor	University of Nevada School of Medicine, Dept. of Pathology	1995-2004
Asst. Professor	Hematology and Blood Bank, San Diego State University, San Diego, CA	1989 - 1998
Chairman	Laboratory Department; Naval Hospital, San Diego, CA. Supervised 20 M.D.s and had authority over 245 technical staff. Also had oversight for research and clinical trials at Naval Clinical Investigation Department.	1989 - 1995
Medical Director	Laboratory Department, 29 Palms, CA	1991 - 1995
Medical Director	Blood Bank; Naval Medical Center, San Diego, CA	1992 - 1995
Head	Microbiology/Immunology Laboratory, Naval Hospital San Diego, CA	1988 - 1995
Lecturer	Parasitology, Immunology, Cytogenetics, University of California at San Diego, San Diego, CA	1982 - 1983
Lecturer	Department of Microbiology, University of Nevada School of Medicine, Reno, NV	1982 - 1983

HOSPITAL STAFF EXPERIENCE

Name	Dates
Baptist Medical Center System, San Antonio, Texas	2003-2005
University of Texas, Tyler, Texas	2003- 2004
East Texas Medical Center, Tyler Texas	2001-2003
Martin Luther King Hospital, Los Angeles, CA	2000-2002
VA Hospital; Reno, NV	1996 - 1999
Vencor Hospitals; San Diego, CA	1994 - 1997
Naval Hospital, San Diego, CA	1984 – 1995

HONORARY DEGREES OR MERIT AWARDS, PRIZES, MEDALS

- Navy Achievements Medal; U.S. Navy; 1999
- Navy Achievements Medal; U.S. Navy; 1992
- American Cancer Scholarship Recipient; Freshman, Sophomore, and Junior years of Medical School; University of Nevada, Reno, NV
- National Student Research Forum Finalist; Galveston, TX; April 28-30, 1982
- Western Student Research Forum Committee member; 1981-1983
- National Fund for Medical Education, Medical Perspective Winner; 1982-1983
  - Development of Continuing Education Program in Infectious Diseases for Rural Nevada

MILITARY/PUBLIC HEALTH SERVICE RECORD

Primary Duty	Branch of Service	Rank
Pathologist	U.S. Navy	Captain, 0-6 – Retired (July 1, 2001)

PROFESSIONAL SOCIETIES AND AFFILIATIONS/SPECIALTY BOARD MEMBERSHIPS

Society	Title	Dates
Advisory Medical Committee, South Texas Blood and Tissue Center	Member	2003-2005
Chairman, Infection Control Committee, Baptist Health Systems, San Antonio, Texas	Chairman	2003-2004
Chairman, Transfusion Committee, Baptist Health Systems, San Antonio, Texas	Chairman	2003-2004
Member, Quality Assurance Committee, Baptist Health Systems, San Antonio, Texas	Member	2003-2005
American Association of Blood Banking	Member	1998-Present
American Society for Microbiology	Member	1975 - Present
American Blood Resources Association (ABRA), Medical Directors Committee	Member	1998 - 2000
International Plasma Products Industry Association (IPPIA), Medical Affairs Committee	Member	1998 - 2000
Southern California Branch of the American Society for Microbiology	Member	1975 - 1991
Advisory Council, ASCP/CAP	Member	1989 - 1995
American Medical Association, Hospital Medical Specialty Section	Member	1989 - 1995

EXPERIENCE

- Medical Physician Representative on Quality Assurance/Risk Management Review Board.
- Conducted Root Cause Analysis on investigations of medical misadventures in hospitals.
- Acted as Expert Witness in East Texas on wrongful deaths in Medical, Surgical, and Infectious Disease Cases.
- Conducted over 500 autopsies in career. 5 cases have been electrical shock autopsies.
- Conduct molecular studies on tissue in black mold exposure cases.
- Researched vaccine for HIV utilizing monoclonal antibodies
- Oversaw pharmacovigilance and database for products in relationship to adverse events, these included life-threatening adverse drug experiences, serious adverse drug experiences and unexpected drug experiences;
- Used MedWatch for reporting adverse events with international clients and domestic clients;
- Acted as Medical Director in a large Pharmaceutical Company (Alpha Therapeutic Corp) to investigate adverse reactions in Medical patients with ITP, HIV, and other immunocompromised situations. Also investigated deaths throughout the US when patient was taking IgIv produced by Alpha Therapeutic Corp.
- Have a working relationship with FDA and Form 3500A;
- Associated with postmarketing 15-day "Alert Reports" and follow-up;
- Associated with "Risk Management" and reporting of all problems to FDA, CDER, and CBER;

- Discussed with Internists/ Surgeons and other physicians problems when they were having problems with products and adverse events that have occurred while patients are under treatment;
- Participated with Regulatory Affairs in labeling and off-label usage and insuring compliance with product insert (circular) that may affect patient health;
- Evaluated trends in adverse events using biostatistics;
- Participated with Regulatory Affairs in communicating with FDA on Adverse Events;
- Evaluated adverse events in clinical trials and report to FDA;
- Utilized Clintrace computer system in pharmaco-vigilance reporting;
- Participated with Program Directors in Clinical Affairs and R&D to evaluate Phase I through IV clinical trials. This included medical oversight and evaluation of usage of product and problems with product;
- Evaluated donors in plasma centers throughout the country for suitability / deferral of donors for plasma donation;
- Founded GLP Compliance Laboratory;
- Knowledge of cGMP;
- Conducted cGMP and GLP audits and validations.
- Written IND protocols.
- Reviewed data for various companies. Especially data compiled from Quintiles Corp.
- Expert witness of Fungal Diseases and Black Mold as well as other Infectious Disease processes.
- Presently act as an international consultant on various aspects of Joint Commission of Hospitals, Bermuda.

PUBLICATIONS

A. Articles:

Hooper, D.G. and DC Hirsh: Effect of resistance possessed by certain enteric microorganisms upon orally inoculated *Salmonella.* Am J Vet Res 37:345, 1976.

Hooper, D.G. and DC Hirsh: Changes of resistance of enteric bacteria in mice given tetracycline in drinking water. Am J Vet Res 38:565, 1977.

Edwards, EA, Kilpaptrick, ME and Hooper, EG: Rapid detection of Pneumococcal antigens in sputum and blood serum using a coagglutination test. Military Medicine, 145:256, 1980.

Safani, M, Kilpatrick, ME, Harrison, WO and Hooper, D.G.: Acute infectious arthritis in an immunosuppressed patient with systemic Lupus erythematosis. Military Medicine, 1982.

Freeman, LD and D.G., Hooper: Brief prophylaxis with doxycline prevents travelers' diarrhea in military personnel visiting Mexico. Gastroenterology, 84:276-80, 1983.

Thomas, W Bevan, H, Hooper, D.G. and Downey, E: Malignant schwannoma of the clitoris in a one-year old child. Cancer, 63:2216-2219, 1989.

Lavin, Bruce S, Putnam, S, Stone, JR, Oldfield, E and Hooper, D.G.: The evaluation of newly developed disk diffusion antibiotic sensitivity of isolates of Neisseria gonorrhoeae, J Clin Microbiology, 30:4, 1992.

Wallace, M. Rockhill, R, Diaz, J and Hooper, D.G.: Varicella immunity and disease in HIV-I positive adults. In de la Marza, L and Peterson, EM (eds): Medical Virology, 10, 1991.

Bylund, David, Ziegner, U and Hooper, D.G.: Review of testing for human immunodeficiency Virus (HIV). Clinics Lab Medicine, 12:305-333, 1992.

Wallace, MR and Hooper, D.G.: Measles immunity in pregnancy. Clin Infec Dis, 14:1262, 1992.

Wallace, MR and Hooper, D.G.: Varicella in pregnancy, the fetus and the newborn: Problems in Management. (Letter), J Infect Dis, 1993.

Horstman, WG, Sands, JP and Hooper, D.G.: Adenomatoid tumor of testicle. Urology, 40:359-361, 1992.

Wallace, M.R., Hooper, D.G., Graves, S.J. and Malone, J.L. Measles Seroprevalence and vaccine response in HIV-Infected adults. Vaccine. 1994, Oct 12 (13): 1222-4.

Wallace, M.R., Hooper, D.G., Pyne, J.M., Graves, S.J. and Malone, J.L. Varicella Immunity and Clinical disease in HIV-Infected Adults. South Med. J. 1994, Jan; 87(1): 74-6.

Ulrich, GG, et al: Cat scratch disease association with neuroretinitis in a 6-year old girl. Opthalmology, 99:246, 1992.

Waeker, J.J., Shope, T.R., Weber, P.A., Buck, M.L., Domingo, R.C., and Hooper, D.G. The Rhino-Probe Nasal curette for detecting respiratory syncytial virus in children. Pediatr. Infec. Dis. J. 1993. Apr; 12(4): 326-9.

Wallace, M.D. and Hooper, D.G. Varicella in pregnancy, the fetus, and the newborn: problems in management. J. Infect. Dis. 1993 Jan; 176(1): 254.

Putnam, S.D., Lavin, B.S., Stone, J.R., Oldfield, 3d, E.C. and Hooper, D.G. Evaluation of the standardized disk diffusion and Agar dilution antibiotic susceptibility test methods by using strains of Neisseria gonorrhoeae from the United States and Southeast Asia. J. Clin. Microbiol. 1992, Apr; 30(4): 974-80.

B. Presentations:

Hooper, D.G. , Ordog, and Wasserberger. Clinical evaluation of surviving twin after fatal case of pulmonary hemosiderosis following Stachybotrys chartarum and other indoor mold product exposure-first case control study. Presented at 5th International Conference on Bioaerosols, Fungi, Bacteria, Mycotoxins, and Human Health. Saratoga Springs, New York, September 10-12, 2003.

Hooper, D.G. "Black Mold- Should we be Concerned... A Perspective Overview. Presented at Biotech Innovations Conference 2003. San Diego, CA September 22-25, 2003.

Thadepalli, H. Appleman, MD, Maidman, JE, Chan, WH, Arce, JJ and Hooper, D.G.: Microbiology of amniotic fluid during intrapartum fetal monitoring. Presented at the 15th Annual Meeting of Antimicrobial Agents and Chemotherapy, Washington, DC, 1975.

Hooper, D.G., Pratt , M. Warnock, G and Super, MA: Dreschlera spicirfica masquerading as a neoplastic process: A review of the literature. Presented at Poster Session. Otolaryngology meeting, 1989.

Mark Walllace, M Hooper, D.G., Putman, S Phifer, S, Weber, P, Rockhill, RC and Diaz-Sola, J: Varicella immunity and disease in HIV positive adults. Presented at Poster Session at the International Symposium on Medical Virology, Newport Beach, California, 1990.

C. Abstracts:

Waecker, NJ, Weber, P, Shope, T, et al: Comparison of rhinoprobe scraper versus nasopharyngeal swab collection method for culture of respiratory viruses. Presented at the 31st Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC), Chicago, IL. Abstract No. 1404, 1991.

D. Books, Chapters:

Thadepalli, H, Huang, JT and Hooper, D.G.: Carbenicillin therapy for anaerobic infections. In Williams, JD and Geddes, AM (eds): Chemotherapy. New York, Plenum Press, NY, 1976 (1975c), pp303-305.

E. Thesis:

Hooper, D.G., Masters Thesis: Changes in levels of resistance of *E. coli* and *Proteus spp.* of the intestinal tract and of *Salmonella typhimurium* from tissues of mice given high and low levels of tetracycline, 1972.

Hooper, D.G., PhD. Thesis: Monoclonal antibodies used as probes to study the cell surface of Neisseria gonorrhoeae, 1982.

RESEARCH/GRANTS/CONTRACTS

Received from Walter Reed Army Institute of Research:

- Rapid Diagnosis of Infectious Agents in HIV Patients - $450,000.
- Cytokines in Long Lived HIV Positive Patients - $600,000.

COMMUNITY AND CIVIC ACTIVITIES

1992 – 1998	Board of Regents, Lutheran High School of San Diego, San Diego, CA
1984 – 1997	Chairman, Aid Association to Lutherans, San Diego, CA
1984 – 1995	Coach, American Youth Soccer Association, San Diego, CA
2000- 2002	Board of Regents, Lutheran High School of San Diego, S.D., CA